Overuse and inappropriate prescribing of proton pump inhibitors in patients with *Clostridium difficile*-associated disease

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Summary

**Background:** *Clostridium difficile* is the most common infectious cause of colitis and has been increasingly diagnosed in hospitalized patients. The number of prescriptions for proton pump inhibitors (PPIs) has also increased significantly over time. Few studies have reported an association between *C. difficile*-associated disease (CDAD) and PPI use.

**Aim:** To assess the extent and appropriateness of PPI prescribing in patients diagnosed with *C. difficile* infection.

**Methods:** We prospectively studied PPI prescriptions in 138 hospitalized patients diagnosed with *C. difficile* infection over a 4-month period.

**Results:** Sixty-four percent (88 of 138) of all patients who developed *C. difficile* infections were on PPIs. A valid indication for PPIs therapy was not apparent in 63% of the patients.

**Conclusion:** There appears to be a widespread and inappropriate use of PPIs in hospital practice. Reduction of unnecessary PPIs use may be an additional strategy to reduce the incidence of this infection.

Introduction

The natural history of *C. difficile*-associated disease (CDAD) is evolving. Recent years have witnessed a significant increase in incidence, severity and mortality of CDAD.¹ Factors associated with altered enteric flora increase the risk of *C. difficile* colonization.² The dominant risk factor is antibiotic use,³,⁴ but other postulated risk factors include advancing age, severe underlying illness,⁵ hospitalization,³ non-surgical gastrointestinal procedures,⁶ anti-neoplastic chemotherapy⁷ and immunosuppressant agents. Gastric acid is important in eliminating ingested bacteria from the digestive tract. Thus it is biologically plausible that raising the pH of the stomach with acid suppressive therapy may result in increased risk of enteric infections including hospital, nursing-home- and community-acquired CDAD.⁸-¹² This finding was supported by a case control study of community-acquired CDAD using a United Kingdom clinical research database.¹⁰ Furthermore, a recent systematic review confirmed an association between acid suppression and an increased risk of enteric infection.¹³

The use of ulcer-healing drugs has increased greatly in recent years and now accounts for nearly 10% of the annual prescribing costs of £4.5 billion in England.¹⁴ The National Institute for Clinical Excellence (NICE) has introduced guidance on the use of Proton Pump Inhibitors (PPIs) in the treatment of *Clostridium difficile* infections were diagnosed by the presence of *C. difficile* toxin in the stools. The appropriateness of prescriptions and relevant investigations were assessed by interview of patients and review of patient records.

**Results:** Sixty-four percent (88 of 138) of all patients who developed *C. difficile* infections were on PPIs. A valid indication for PPIs therapy was not apparent in 63% of the patients.

**Conclusion:** There appears to be a widespread and inappropriate use of PPIs in hospital practice. Reduction of unnecessary PPIs use may be an additional strategy to reduce the incidence of this infection.
of dyspepsia to the National Health Service (NHS).\textsuperscript{15} However, the introduction of these guidelines appeared to have little impact on clinical practice. In fact, PPI prescriptions continued to increase. We have observed an increase in the incidence of \textit{C. difficile} diarrhoea, coincident with increased use of PPIs. Therefore, an audit of appropriateness of PPI prescribing in patients developed with \textit{C. difficile} diarrhoea in a large University hospital was undertaken.

### Patients and methods

A prospective study was conducted at a tertiary referral hospital in Manchester for a period of 4 months. \textit{Clostridium difficile} infections were diagnosed in patients who had a history of diarrhoea (defined as two or more loose bowel movements per day) and the presence of \textit{C. difficile} toxin in the stool. All hospital in-patients diagnosed with \textit{C. difficile} infection reviewed. Cases were identified from laboratory and infection control team records. We have studied drug prescription charts, Accident and Emergency admission cards (except paediatrics and gynaecology) for use of antisecretory drugs (PPIs and histamine 2 receptor antagonists) in addition to the patients’ medical notes. Patients on antisecretory drugs were interviewed to obtain information regarding the type, dose, duration of treatment, indication for use and investigations performed relevant to PPIs prescription and \textit{Helicobacter pylori} eradication. Where possible, the origin of prescription was also ascertained from the patient. Data were also collected from the patient’s medical notes to identify the indication for treatment, timing of the endoscopic procedure, endoscopic and clinical diagnosis and \textit{H. pylori} status. We considered the guidance issued by NICE on the use of PPIs in the treatment of dyspepsia as appropriate for initiation of antacid therapy (Table 1).

### Statistics

Statistical analysis was performed using the SPSS (Version 11). Differences between patient groups were tested for statistical significance using $\chi^2$ analysis. A $P$-value <0.05 was considered significant.

### Results

A total of 138 patients developed with \textit{C. difficile} infections over a period of 4 months and diagnosed by positive \textit{C. difficile} toxin assay were reviewed. The mean age was 76 (range 35–97 years) years. Forty-nine (55.7\%) female and 39 (44.3\%) male hospitalized patients were on PPIs. Seventy-five patients were prescribed a PPI either by their GP or a hospital physician but the source of the prescription could not be ascertained in 12 patients. Only 4 patients started on PPI during this admission. Omeprazole (70\%) was clearly the most PPI prescribed followed by lansoprazole (19\%),

### Table 1  NICE issues guidance on PPIs for dyspepsia

<table>
<thead>
<tr>
<th>NICE issues guidance on PPIs for dyspepsia</th>
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<tbody>
<tr>
<td>The NICE guidelines for dyspepsia recommend that all PPIs are well tolerated and have similar efficacy so the least expensive PPIs should be used:</td>
</tr>
<tr>
<td>• Short-term treatments for gastric and duodenal ulcers.</td>
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<tr>
<td>• In combination with antibacterial chemotherapy for the eradication of \textit{H. pylori}.</td>
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<tr>
<td>• An initial short course of a PPI is the treatment of choice in gastro-oesophageal reflux disease with severe symptoms.</td>
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<tr>
<td>• Patients with endoscopically confirmed erosive or ulcerative oesophagitis, or oesophagitis complicated by stricture.</td>
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<tr>
<td>• Prevention and treatment of NSAID-associated ulcers</td>
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<tr>
<td>• Treatment of the Zollinger-Ellison syndrome.</td>
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<tr>
<td>• Management of dyspepsia in adults in primary care as follow:</td>
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<tr>
<td>o Un-investigated dyspepsia:</td>
</tr>
<tr>
<td>• The duration of treatment should be only for between 2 and 4 weeks and the patient then reviewed if over 45 years old or if symptoms recur or persist.</td>
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<tr>
<td>o Gastro-oesophageal reflux disease:</td>
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<tr>
<td>• Treat with a full-dose proton pump inhibitor for 1 or 2 months</td>
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<tr>
<td>• If symptoms recur following initial treatment, then give a proton pump inhibitor at the lowest dose possible to control symptoms, with a limited number of repeat prescriptions</td>
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<tr>
<td>• In cases of severe GORD, oesophageal hemorrhage or stricture of Barrett’s oesophagus, then the full treatment dose of PPI should be continued.</td>
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<td>o Barrett’s oesophagus:</td>
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<tr>
<td>• Long-term PPI therapy is required.</td>
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<td>• Twice daily PPI therapy may be recommended for patients who do not respond clinically to once daily therapy.</td>
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pantoprazole (5%) and other antisecretory medications (6%). Ninety percent of the patients were on one of these drugs for >4 weeks, 50% for >6 months and 35% for >12 months. The duration of therapy was not significantly related to the age of the patient (P = 0.07).

An appropriate indication for prescription of PPIs was not apparent in 47 (53.4%) patients. There was no relevant history and patients gave no history of dyspepsia. Relief of non-specific abdominal symptoms or indeterminate chest pain was the main unapproved indication for PPIs therapy in 31 patients. PPIs were co-prescribed with low dose aspirin in nine patients and given to two patients with warfarin with no history of dyspepsia or evidence of previous peptic ulcer disease. Five patients had continued to receive PPIs long term after H. pylori eradication, although they had no symptoms. PPI therapy was prescribed for an approved indication in 34 (38.6%) patients as shown in Table 2. Seven patients were having PPI for unknown reasons.

### Discussion

An association between acid suppressive therapy and *C. difficile* diarrhoea or colitis has been suggested in previous studies.10,16 This study was designed to assess the extent and appropriateness of PPIs prescribing in patients who developed *C. difficile* infection. A study from UK showed that between 1992 and 1995 the total volume of prescribing for PPIs increased 10-fold.17 In our study around 63.7% of patients developed or admitted with *C. difficile* infection were on PPIs and documented in the treatment chart. The higher percentage of patients on PPI therapy in our study may simply reflect the time trend in prescribing since then with a rapidly increasing rate of PPIs prescribing in both primary and secondary care. In only 38.6% of PPIs prescribing was appropriate according to NICE recommendations. Our results are in agreement with previous studies which show that 63.2% of studied patients had no appropriate indication for use of PPIs.18 Furthermore, 1 year review of all out-patient prescriptions at an urban county teaching hospital in the US showed that 56% of omeprazole prescribing was inappropriate.19

PPIs are frequently prescribed for non-specific abdominal or chest pain and the prescription is generally continued if a patient is admitted to hospital.20,21 For instance, Bashford et al.17 found that prescribing of PPIs for unlicensed indications, such as non-specific abdominal pain or mild dyspepsia accounted for 46% of new prescriptions in 1995. Furthermore, concurrent PPI use with prophylactic aspirin in patients with significant gastrointestinal disturbance due to aspirin, or those with a history of peptic ulcer disease is a well recognized practice. However, this indication is not approved by NICE. Often the patient has been receiving PPI treatment for a long time and neither the primary care doctors nor the admitting hospital practitioners have questioned the indication for its continuing use. Concern has been raised that many patients may have been treated with these expensive drugs without life-style modifications (e.g. weight loss, stopping smoking, reducing alcohol and fat intake) or simpler, less expensive treatments.22

It is worth mentioning that we were unable to identify the use of non-prescription medications, such as antacids and low-dose histamine 2 receptors antagonists (e.g. ranitidine, 75 mg). However, these drugs have less influence on gastric pH than PPIs. Despite this limitation, the findings of this study provide further insight into use of PPIs therapy and current practice patterns among patients who developed *C. difficile* infection. Thus, it is apparent that NICE guidelines at present are not being followed, calling into question their place in clinical practice and lack of enforcement. The best means of promoting adherence to expert recommendations has yet to be determined but passive dissemination of written guidelines can be ineffective as proved in previous studies.

**Conflict of interest:** None declared.
References


